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(54) **Enhancer of anti-tumour effect.**

(57) N^6-acylated 3'-deoxyadenosines or phosphates thereof are disclosed as being effective for enhancing anti-tumor effect afforded by irradiation of or administration of an anti-tumor pharmaceutical to tumor-bearing animals.

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ENHANCER OF ANTI-TUMOR EFFECT

BACKGROUND OF THE INVENTION

Field of the art

This invention relates to an enhancer of anti-tumor effect.

In the art of treatment of tumors, there have been many developments from various aspects. In radiotherapy, as a branch of these developments, there have also been attempts to improve the results of therapy. As one method, it is proposed to improve geometrical dose distribution by use of such methods as radiation of accelerated heavy ion particles or π meson. Another approach now under the development is to enhance selectively the sensitivity of tumor cells under hypoxic conditions, which are most resistant to radiotherapy among tumors, by utilizing a hypoxic cell sensitizer. Alternatively, combination treatments incorporating a method utilizing other anti-tumor factors, such as hyperthermia or chemotherapy have been attempted.

However, in the method for improvement of geometrical dose distribution, it is necessary to use enormous funds for installation of an accelerator and auxiliary equipments necessary for practicing the method as well as a large personnel including expert engineers and physicians. Other methods also involve drawbacks such as great damage to normal cells. For example, misonidazole, which is a hypoxic cell sensitizer, has neurotoxicity, and hence it is difficult to administer it in a large quantity, whereby no great radiosensitizing effect can be expected at concentrations available in clinical use, its effect being small in a low dose range (less than 1,000 rad) as employed in a routine therapy.

On the other hand, in the field of chemotherapy of tumors, multiple anti-tumor agents have been combined to be used for the following purposes and effects:

1) By using in combination a number of different agents

selected from those of alkylating agents, antimetabolites, antibiotics and alkaroids, which show mutually no cross resistancy and are different in mechanism of action, the anti-tumor effect can be enhanced additively or synergistically against tumors which are composed of a mixture of tumor cells different in sensitivity to various agents.

2) By using in combination anti-tumor agents different in the way they attack tumor cells which are proliferating at random, various stages in the cell cycle of tumor cells can be widely attacked to ensure complete killing of tumor cells.

3) By using not only agents different in mechanism of action but also those having relatively similar mechanisms of action, a synergistic effect can be expected. For example, by using in combination a number of agents which are blocking a series of steps participating in DNA synthesis, a strong synergistic effect can be exhibited.

4) Each anti-tumor agent has its specific side effect. Thus, by using in combination a number of agents with different side effects each in a dosage less than the limit above which side effects appear, the anti-tumor effect can be expected to be increased additively or synergistically while the side effects are dispersed.

By such a multi-agent combination treatment, it has been made possible to obtain an effect which could not be produced by using a single anti-tumor agent. However, each of the agents used in combination in such an application is an anti-tumor agent which can be independently used.

There have also been various attempts to use in combination with an anti-tumor agent a compound which does not per se have an anti-tumor effect for the purpose of strengthening the effect of the anti-tumor agent by preventing the anti-tumor agent from being inactivated in bodies. For example, it is known to use cytidine or uridine in combination with 1-β-D-arabinofuranosylcytosine (hereinafter referred to as "araC"), as disclosed in Japanese Patent Laid-Open Publication No. 24150/1980. It is also known to use

tetrahydrouridine, which is an inhibitor against cytidine-deaminase, in combination with araC, as disclosed in Cancer Research Vol. 30, p.2166 - 2172, 1970. Further, there is known another method wherein 5-fluorouracil (hereinafter referred to as "5-FU") or a derivative thereof is combined with a pyrimidine compound such as, for example, uracil, cytosine, thymine, orotic acid, 5-bromouracil, 5-iodouracil, 1-acetyluracil, 1-(2-tetrahydrofuryl)-uracil, 3-benzoyluracil, 1-cyclohexycarbamoyluracil, 1-n-hexy-carbamoyluracil, uridine, 2'-deoxyuridine, 5-bromo-2'-deoxyuridine, cytidine, or 2'-deoxycytidine.

On the other hand, in the field of radiotherapy, the tumor cells with radioresistance under hypoxic conditions are at a quiescent stage, and also there has been observed a phenomenon wherein potentially lethal damage repair (hereinafter referred to as "PLDR") is markedly manifested particularly in the cells at a quiescent stage. By inhibiting PLDR of such tumor cells, it is possible to increase the therapeutical effect of radiotherapy. We have investigated the possibility of radio-sensitization by inhibiting PLDR with the use of a chemical. During the course of this investigation, 3'-deoxyadenosine (cordycepin, herein referred to as "3'-dAdo") was confirmed to have a PLDR-inhibiting ability. However, 3'-dAdo is readily inactivated by adeno-sinedeaminase in bodies. We found that the PLDR-inhibiting ability of 3'-dAdo can be strengthened and prolonged by using in combination therewith 2'-deoxycoformycin, which is an inhibitor against adenosinedeaminase. However, there is also a report that 2'-deoxycoformycin may cause damage to the immune systems, and 3'-dAdo is also known to have various side effects. Thus, it would be very desirable to have a radiosensitizing substance which is more stable, lower in toxicity, and more effective than 3'-dAdo.

The PLDR phenomenon of tumor cells is observed not only in the field of radiotherapy but also in the treatment with a chemotherapeutics such as Bleomycin or 5-FU, as reported in the Journal of the National Cancer Institute, Vol. 50, No.2,

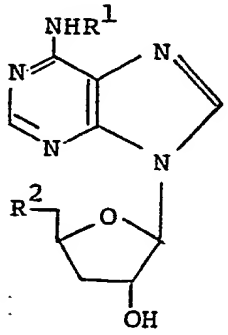
p.529 - 533, 1973. Accordingly, a pharmaceutical agent capable of inhibiting repair from damage of tumor cells can also enhance the anti-tumor effect not only of radiation but also of chemotherapeutics.

SUMMARY OF THE INVENTION

In view of the above described state of the art, we have made extensive studies with the aim of obtaining a radiosensitizing agent having a PLDR-inhibiting activity with low toxicity and good stability. As a result, it has now been found that a N^6-acyl derivative of 3'-dAdo has a PLDR-inhibiting activity and excellent radiosensitizing activity. It has also been found that these N^6-acyl-3'-dAdo derivatives can also exhibit excellent effect in strengthening anti-tumor effect in treatment of malignant tumors with chemotherapeutics. The present invention has been accomplished on the basis of such findings. Thus, the present invention provides a pharmaceutical agent to be used for strengthening the anti-tumor effect in treatment of malignant tumors by irradiation and/or an anti-tumor agent.

While the mechanism in which the pharmaceutical agent of the present invention acts on tumors has not yet been completely clarified, the present pharmaceutical agent may be considered to be a pharmaceutical which will enhance the anti-tumor effect of radiation or a chemotherapeutic through acting (e.g. inhibitory action) on changes in nucleic acid metabolism such as PLDR (e.g. repair of damage in DNA) caused by treatment with radiation or chemotherapeutics.

In one aspect of the present invention, the present invention relates to a preparation of an enhancer of anti-tumor effect which comprises an N^6-acyl-3'-deoxyadenosine derivative of a formula (I):



(I)

wherein R^1 represents an acyl group and R^2 represents a hydroxyl group, a phosphoric acid residue or a phosphoric acid salt residue,
and a pharmaceutically acceptable carrier.

In another aspect of the present invention, the present invention relates to a chemotherapeutic composition for treating tumors which comprises an anti-tumor agent, an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxyadenosine derivative of the formula (I) and a pharmaceutically acceptable carrier.

In still another aspect of the present invention, the present invention relates to a method for enhancement of anti-tumor effect, which comprises administering to a tumor-bearing animal under an anti-tumor treatment an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxyadenosine derivative of the formula (I).

The term "animal" as herein used means a human being or a lower animal.

The wording "under an anti-tumor treatment" means the state wherein a tumor-bearing animal is being subjected to physical, chemical or physicochemical treatment for suppressing tumors or the state wherein there is retained in that animal an influence due to such a treatment. Accordingly and more specifically, the enhancer is administered to the animal before, simultaneously with, or after irradiation when the anti-tumor treatment comprises irradiation to a tumor site of the animal. The enhancer is administered before, simultaneously with, or after administration of an anti-tumor agent when the anti-tumor treatment comprises administration of an anti-tumor agent.

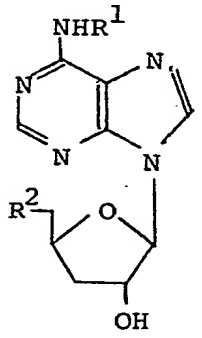
In a further aspect of the present invention, it relates to a method for therapy of tumors which comprises administering to a tumor-bearing animal under an anti-tumor treatment an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxyadenosine derivative of the formula (I).

DETAILED DESCRIPTION OF THE INVENTION

Enhancers

The enhancers in accordance with the present invention are N^6-acyl-3'-deoxyadenosine (dAdo) derivatives of a specified group. The enhancers may alternatively be regarded as repair-inhibiting agents, and both terms are herein used interchangeably.

The N^6-acyl-3'-dAdo derivatives are represented by the formula:



(I)

wherein R^1 represents an acyl group which preferably contains 2 to 26 carbon atoms, more preferably 2 to 22 carbon atoms and R^2 hydroxyl group, phosphoric acid residue or a phosphoric acid salt residue.

More specifically, typical examples of the compounds may include N^6-acetyl-3'-dAdo, N^6-propionyl-3'-dAdo, N^6-butyryl-3'-dAdo, N^6-hexanoyl-3'-dAdo, N^6-heptanoyl-3'-dAdo, N^6-octanoyl-3'-dAdo, N^6-nonanoyl-3'-dAdo, N^6-decanoyl-3'-dAdo, N^6-lauroyl-3'-dAdo, N^6-palmitoyl-3'-dAdo, N^6-stearoyl-3'-dAdo, and 5'-phosphoric acid ester derivatives thereof. When R^2 is a phosphoric acid salt, the kind of the salt may be any of those which are pharmaceutically acceptable, including, for example, alkali metal salts such as those of lithium, sodium, potassium, etc., alkaline earth metal salts such as those of calcium, magnesium, etc., and ammonium salts.

An N^6-acyl-3'-dAdo derivative can be prepared according to the method in which 3'-dAdo or its 5'-phosphoric acid

ester is allowed to react in a pyridine type solvent with an acid anhydride or an acid halogenide corresponding to the acyl group in a desired compound to synthesize an N^6, $O^{2'}$, $O^{5'}$-triacyl-3'-dAdo or an N^6, $O^{2'}$-diacyl-3'-dAdo-5'-phosphate, which reaction is followed by hydrolysis of the intermediate to eliminate the acyl groups at the sugar moieties.

Enhancement of anti-tumor effect

The pharmaceutical agent according to the present invention, when it is a preparation of an enhancer of anti-tumor effect which is free of an anti-tumor agent, may be used for the purpose of enhancing the anti-tumor effect in the treatment of a malignant tumor, for which radiotherapy or chemotherapy by anti-tumor agents is to be applied, in combination with the treatments by these therapeutical methods.

In the case where the pharmaceutical agent of the present invention is used as a radiosensitizing agent for the purpose of enhancing the effect of radiotherapy, it may be administered before or after exposure, or even during exposure, if the occasion permits it, to the irradiation in radiotherapy. As to radiotherapy per se, the use of specific method and conditions is not required, but conventional radiotherapy techniques may be employed. By the use of the enhancer of the present invention in combination, it has become possible to apply radiotherapy with irradiation in the region of lower dosage than in the prior art. As the ionizing radiations for radiotherapy, those generally employed such as X-rays, lineac high energy X-rays, betatron 32 MeV electron beams or ^{60}Co-γ-rays may be used.

When used for the purpose of enhancing the anti-tumor effect in chemotherapy by an anti-tumor agent, the enhancer of the present invention may be administered simultaneously with, after, or before administration of the anti-tumor agent. Anti-tumor agents, of which anti-tumor effects are to be enhanced by the pharmaceutical agent of the present invention, are exemplified typically by substances having activity similar to irradiations, including also those which can induce

changes in nucleic acid metabolism such as repair phenomenon like PLDR in tumor cells on which an N^6-acyl-3'-dAdo can act after treatment therewith. Examples of anti-metabolites are methotrexate; 6-mercaptopurine; 5-FU and its derivatives, such as, for example, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, 1-β-D-arabinofuranosyl-5-fluorocytosine, 1-(2-tetrahydrofuryl)-5-fluorouracil (hereinafter referred to as "FT-207"), 1-(n-hexylcarbamoyl)-5-fluorouracil, 1-ethoxymethyl-5-fluorouracil, 1-ethoxycarbonyl-5-fluorouracil, and 5-fluoro-5'-deoxyuridine; and araC and its derivatives, such as, for example, cyclocytidine, N^4-palmitoyl araC, N^4-stearoyl araC, N^4-behenoyl araC, araC-5'-phospho-stearyl ester, and araC-5'-phospho-oleyl ester may be mentioned. Examples of anti-tumor antibiotics are Bleomycin; Neocarzinostatin; and Anthracycline type antibiotics, such as, for example, Daunomycin, Adriamycin, and Aclacinomycin. Examples of alkylating agents include nitrosourea, such as, for example, ACNU, BCNU, CCNU, MCCNU; 3'-[3-(2-chloroethyl)-3-nitrosoureido]-3'-deoxythymidine; and 3'-(3-methyl-3-nitrosoureido)-3'-deoxythymidine. These anti-tumor agents may be administered by any method and in any dosage which are not specifically limited in combination with the enhancer of the present invention, but optimum conditions may suitably be selected for each agent used.

The pharmaceutical agent according to another aspect of the present invention, when it is a chemotherapeutic composition, comprises an anti-tumor agent and the enhancer of anti-tumor effect in combination. Anti-tumor agents and the enhancers of anti-tumor effect to be used are set forth hereinabove.

The pharmaceutical agents according to the present invention, irrespective of whether they are enhancers of anti-tumor agent or chemotherapeutic compositions, may comprise a pharmaceutically acceptable carrier. Examples of such carriers include lactose, magnesium stearate, talc, corn starch, "Witepsol" (Tradename, supplied by Dynamit Nobel Co., Germany), crystalline cellulose, distilled water, alcohols, and the like.

The method for administration of the pharmaceutical agent

of the present invention may in general be either systemic administration or local administration. Various dosage unit forms can be selected depending on the purposes of therapy and the methods of administration. For example, as the form for systemic administration, an oral administration form such as tablet, capsule, granule or solution, or a non-oral administration form such as injection, suppository, etc., can be used. On the other hand, as a local administration form, a slow-releasing-capsule, an ointment or an injection can be used. In the preparing of such a dosage unit form, it is possible to make a preparation according to a conventional method using a pharmaceutically acceptable carrier. Various modifications in preparation suitable for the object of the present invention may also be utilized.

The N^6-acyl-3'-dAdo derivative of the present invention is used in an amount effective for enhancement of anti-tumor activity. More specifically, the dosage of the pharmaceutical agent of the present invention per day, which may slightly differ depending on the active ingredient employed, in general, is desirably 20 to 3,000 mg for an oral administration, 0.5 to 500 mg for an injection, and 20 to 2,000 mg for a suppository, as determined from basic experiments on anti-tumor effectiveness. The optimum effective amount should be determined by judgement of a physician according to the irradiation used, its dosage, the anti-tumor agent used, its dosage, the conditions of disease, the affected part, etc.

The pharmacological effects of the pharmaceutical agents of the present invention are shown below with data from the tests of radiosensitizing effect thereof.

Experiment 1

Radiosensitizing effect on the tumor cells in culture

Cells under stationary phase, prepared by planting 2×10^5 cells/well of Chinese hamster-HA-1 cells in a multi-well dish and exchanging cultural medium every day starting on the third day and thereafter were irradiated with 1,000

R of X-rays. Immediately after radiation, N^6-butyryl-3'-dAdo in Hanks' balanced salt solution were administered. Then, after elapse of various times, the cells were taken off with trypsin, and a suitable number of cells were transferred into petri dishes for testing colony forming ability and plating efficiencies. The percentages of survival were calculated with corrections by the plating efficiencies with the pharmaceutical agents alone. The results are shown in Table 1.

Table 1: Radiosensitizing effect of the enhancers in Chinese hamster-HA-1 cells

Enhancer	Treatment conc. µg/ml	Plating efficiency (%)			
		Immediately after irradiation	After 1 hour	After 4 hours	After 7 hours
N^6-butyryl-3'-dAdo	0	0.94	2.7	3.6	5.0
	40		1.4	2.2	2.4

As is apparent from Table 1, N^6-butyryl-3'-dAdo is found to inhibit repair (PLDR) after irradiation with X-rays. Substantially no toxicity was observed, as examined by plating efficiencies.

Experiment 2

Radiosensitizing effect on experimental tumor in mice

EMT-6 tumor cells (2×10^5) were inoculated intradermally into the right thighs of BALB/c-strain female mice (8 weeks old, 6 or more mice for each group). When the tumor size reached 5.5 to 7.5 mm in diameter after inoculation of the tumor cells, local irradiation with a 32 MeV electron beam was carried out at 1,500 rad under no anesthesia and thereafter N^6-butyryl-3'-dAdo dissolved in physiological saline solution, was administered intraperitoneally to each mouse in 100 mg/kg. On the 9th day and 20th day after these treatments, t' tumor sizes were measured in tri-dimensional

diameters, and compared with the control group with respect to the following items:

1) Mean tumor diameter = $\left(\frac{\text{Maximum longitudinal diameter} + \text{Maximum lateral diameter} + \text{Maximum height (diameter)}}{3}\right)$

2) Diameter ratio = $\frac{\text{Mean tumor diameter}}{\text{Mean tumor diameter at the time of irradiation}}$

The results are shown in Table 2, in which "cure" means that the tumors completely vanished during the observation period.

Table 2: Sensitizing effect of enhancer on X-ray therapy of EMT-6 tumors

Treatment	Mean tumor diameter at the time of irradiation (mm)	9 days after treatment			20 days after treatment			
		Mean tumor diameter (mm)	Diameter ratio	Sensitizing effect *	Mean tumor diameter (mm)	Diameter ratio	Sensitizing effect *	Cured cases
Irradiation (1500 rad) alone (n = 8)	6.61±0.57	6.40±0.93	0.97±0.07	1	7.83±2.01	1.11±0.24	1	4/8
Irradiation + N^6-butyryl-3'-dAdo (n = 9)	6.43±0.29	5.36±1.13	0.83±0.18	0.86	0.0±0.0	-	0.00	9/9

$$\text{* Sensitizing effect} = \frac{\text{Diameter ratio when the pharmaceutical agent of the invention is used}}{\text{Diameter ratio when the pharmaceutical agent of the invention is not used (irradiation alone)}}$$

Experiment 3

Radiosensitizing effect on experimental tumors in mice

EMT-6 tumor cells (2×10^5) were inoculated intradermally into the right thighs of BALB/c-strain female mice (8 weeks old). When the tumor sizes reached 5.5 to 8.0 mm after inoculation of the tumor cells, irradiation was locally carried out with 1,000 rad to 2,700 rad of 32 MeV electron beam under no anesthesia, and thereafter 3'-dAdo and N^6-butyryl-3'-dAdo, each dissolved in physiological saline solution, were administered intraperitoneally in a dose of 100 mg/kg. After the treatments, observation was continued for longer than 90 days, and the cure percentages were determined for comparison with the control group.

1) Cure percent = $\frac{\text{Cure numbers on 90th day}}{\text{Number of mice at irradiation}} \times 100$

2) TCD_{50} = 50% Tumor control dose

The results are shown in Table 3.

Table 3 Sensitizing effect of enhancer on X-ray therapy of EMT-6 tumors

Treatment	Cure number/Number treated (%)				TCD_{50}
	1,000 rad	1,500 rad	2,100 rad	2,700 rad	(ratio)
Control	1/23(4%)	8/44(18%)	9/24(38%)	13/28(47%)	2400(1.0)
3'-dAdo	3/18(17)	14/29(48)	11/14(79)	10/15(67)	1600(0.67)
N^6-butyryl-3'-dAdo	6/15(40)	13/20(65)	14/15(93)	16/16(100)	1080(0.45)

Experiment 4

Radiosensitizing effect on experimental tumors in mice

RIF_1 tumor cells (2×10^5) were inoculated intradermally into the right thighs of C3H/Heston-strain female mice (8 weeks old). When the tumor sizes reached 6.0 to 10.0 mm after inoculation of the tumor cells, irradiation was carried out with 2,500 rad/min. of an electron beam, and thereafter N^6-acetyl-3'-dAdo, N^6-butyryl-3'-dAdo, N^6-hexanoyl-3'-dAdo, and N^6-

octanoyl-3'-dAdo, each dissolved in physiological saline solution, were administered intraperitoneally in a dose of 100 mg/kg. After the treatments, the tumor sizes in terms of diameters in three-axial directions were measured on the 10th day and the 20th day (9th day and the 21st day only in case of N^6-butyryl-3'-dAdo). The results are shown in Table 4.

Table 4: Sensitizing effect of enhancer on X-ray therapy of RIF_1 tumors

Treatment	Mean tumor diameter at the time of irradiation (mm)	10th day after treatment			20th day after treatment		
		Mean tumor diameter (mm)	Diameter ratio	Sensitizing effect	Mean tumor diameter (mm)	Diameter ratio	Sensitizing effect
Irradiation (2500 rad) alone (n = 7)	6.83±0.52	8.07±0.79	1.18±0.06	1	12.00±0.65	1.78±0.07	1
Irradiation + N^6-acetyl-3'-dAdo (n = 7)	7.03±0.39	7.86±0.55	1.12±0.06	0.95	10.39±0.51	1.49±0.06	0.84
Irradiation + N^6-butyryl-3'-dAdo (n=7)	7.44±0.19	6.71±0.63	0.90±0.08	0.76	10.28±0.36	1.35±0.08	0.76
Irradiation + N^6-hexanoyl-3'-dAdo (n=7)	7.20±0.46	7.90±0.47	1.11±0.05	0.94	10.37±0.42	1.46±0.05	0.82
Irradiation + N^6-octanoyl-3'-dAdo (n=7)	7.23±0.30	7.50±0.37	1.04±0.04	0.88	9.61±0.46	1.33±0.02	0.75

Experiment 5

Enhancement of the effect of anti-tumor agents on experimental tumors in mice

EMT-6 tumor cells (1×10^6) were inoculated intradermally into the right thighs of BALB/c-strain mice (8 weeks old). On the 12th day after inoculation of the tumor cells and thereafter, each chemical in a physiological saline solution was administered intrapenitoneally to each mouse four times a week in the indicated doses for respective agents. The pharmaceutical agents of the present invention were administered one hour after administration of the anti-tumor agents. After commencement of the treatment with pharmaceutical agents, the tumor sizes were measured every other day and compared with those of the control group.

The results are given in Table 5.

Table 5: Enhancing effect of enhancer on chemotherapy of EMT-6 tumors

Treatment with anti-tumor agent	Treatment with pharmaceutical of the invention	Mean tumor diameter immediately before treatment (mm)	14th day after treatment		
			Mean tumor diameter (mm)	Diameter ratio (mm)	Enhancing effect
Control (n = 6)	-	6.00±0.89	9.20±1.78	1.57±0.40 (1.00)	
- (n = 5)	N^6-butyryl-3'-dAdo (50mg/kg x 7)	7.60±0.56	9.92±2.45	1.36±0.32 (0.87)	
FT-207 100mg/kg x 7 (n = 4)	-	6.68±1.04	7.80±1.64	1.19±0.26 (0.76)	
FT-207 100mg/kg x 7) (n = 5)	N^6-butyl-3'-dAdo (50mg/kg x 7)	6.88±0.37	6.72±1.69	0.97±0.23 (0.62)	0.94

$$\text{Enhancing effect} = \frac{\text{Diameter ratio when anti-tumor agent and pharmaceutical of the invention are used in combination}}{\text{(Diameter ratio when anti-tumor agent alone is used) x (Diameter ratio when pharmaceutical of the invention alone is used)}}$$

Experiment 6

Acute toxicity test

Various quantities of N^6-butyryl-3'-dAdo were administered intraperitoneally to ICR mice (male, 8-weeks old, 10 mice for each group) in doses of 250 mg to 1,000 mg/kg, and the mice were subjected to observation for a week. As a result, the LD_{50} of N^6-butyryl-3'-dAdo was found to be 710 mg/kg (640 mg/kg-788 mg/kg : 95% confidence limit). The LD_{50}(i.p.) of 3'-dAdo was 280 mg/kg (241.4 mg/kg - 324.8 mg/kg : 95% confidence limit).

Preparation 1

N^6-butyryl-3'-dAdo	100 mg
Lactose	170 mg
Magnesium stearate	3 mg
Crystalline cellulose	57 mg
	330 mg/capsule

Capsules are prepared according to the above formulation.

Preparation 2

N^6-butyryl-3'-dAdo	100 mg
Lactose	100 mg
Magnesium stearate	2 mg
Talc	3 mg
Hydroxypropylmethyl cellulose	10 mg
	215 mg/tablet

Tablets are prepared according to the above formulation.

Preparation 3

N^6-butyryl-3'-dAdo	500 mg
Lactose	240 mg
Corn starch	250 mg
Hydroxypropylmethyl cellulose	10 mg
	1,000 mg/package

Granules are prepared according to the above formulation.

Preparation 4

N^6-butyryl-3'-dAdo	100 mg
Tris-amino methane	220 mg
Distilled water for injection	appropriate amount
	10 ml/ampoule

Injections are prepared according to the above formulation.

Preparation 5

N^6-butyryl-3'-dAdo	500 mg
Witepsol W-35	1,500 mg
	2,000 mg/suppository

Suppositories are prepared according to the above formulation.

Preparation 6

N^6-butyryl-3'-dAdo	100 mg
FT-207	100 mg
Lactose	100 mg
Crystalline cellulose	57 mg
Magnesium stearate	3 mg
	360 mg/capsule

Capsules are prepared according to the above formulation.

Preparation 7

N^6-butyryl-3'-dAdo	100 mg
FT-207	100 mg
Lactose	33 mg
Crystalline cellulose	15 mg
Magnesium stearate	2 mg
Talc	3 mg
Corn starch	14 mg
Hydroxypropylmethyl cellulose	10 mg
	277 mg/tablet

Tablets are prepared according to the above formulation.

Preparation 8

N^6-butyryl-3'-dAdo	100 mg
FT-207	200 mg
Lactose	580 mg
Corn starch	90 mg
Hydroxypropylmethyl cellulose	30 mg
	1,000 mg/package

Parvules are prepared according to the above formulation.

Preparation 9

N^6-butyryl-3'-dAdo	50 mg
FT-207	100 mg
Sodium carbonate	440 mg
Sodium hydroxide	35 mg

Distilled water for injection	appropriate amount
	10 ml/ampoule

Injections are prepared according to the above formulation.

Preparation 10

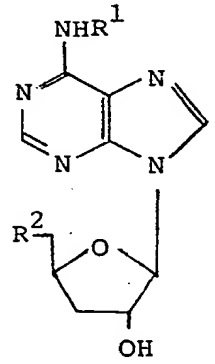
N^6-butyryl-3'-dAdo	300 mg
FT-207	750 mg
Witepsol W-35	950 mg
	2,000 mg/suppository

Suppositories are prepared according to the above formulation.

WHAT IS CLAIMED IS:

1. A preparation of an enhancer of anti-tumor effect which comprises:

an N^6-acyl-3'-deoxyadenosine derivative represented by the formula:



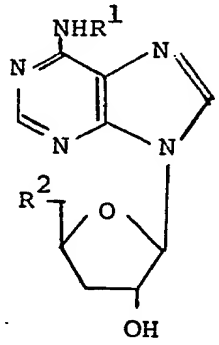
wherein R^1 represents an acyl group and R^2 represents a hydroxyl group, a phosphoric acid residue or a phosphoric acid salt residue; and

a pharmaceutically acceptable carrier.

2. The preparation as claimed in claim 1 in which the substitutent R^1 contains 2 to 26 carbon atoms.

3. The preparation as claimed in claim 1 in which the substituent R^1 contains 2 to 22 carbon atoms.

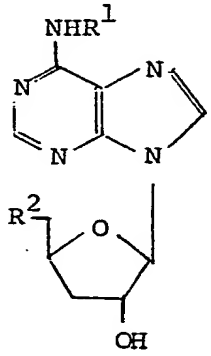
4. A chemotherapeutic composition for treating tumors which comprises an anti-tumor agent, an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxyadenosine derivative represented by the formula:



wherein R^1 represents an acyl group and R^2 represents a hydroxyl group, a phosphoric acid residue or a phosphoric acid salt residue, and a pharmaceutically acceptable carrier.

5. The chemotherapeutic composition for treating tumors as claimed in claim 4 in which the anti-tumor agent is selected from the group consisting of anti-metabolites, anti-tumor antibiotics and alkylating agents.

6. A method of enhancement of anti-tumor effect which comprises administering to a tumor-bearing animal under the anti-tumor treatment an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxyadenosine derivative represented by the formula:



wherein R^1 represents an acyl group and R^2 represents a hydroxyl group, a phosphoric acid residue or a phosphoric acid salt residue.

7. The method of enhancement of anti-tumor effect as claimed in claim 6 in which the anti-tumor treatment comprises irradiation of a tumor site of the animal, and the enhancer is administered to the animal before, simultaneously with, or after the irradiation.

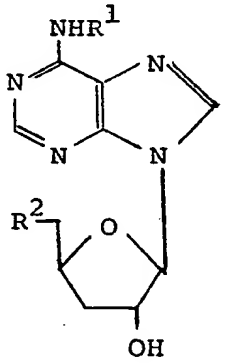
8. The method of enhancement of anti-tumor effect as claimed in claim 7 in which the enhancer is administered to the animal before the animal is subjected to the irradiation.

9. The method of enhancement of anti-tumor effect as claimed in claim 7 in which the enhancer is administered to the animal after the animal has been subjected to the irradiation.

10. The method of enhancement of anti-tumor effect as claimed in claim 6 in which the anti-tumor treatment comprises administration to the animal of an anti-tumor agent, and the enhancer is administered to the animal before, simultaneously with, or after the administration of the anti-tumor agent.

11. The method of enhancement of anti-tumor effect as claimed in claim 10 in which the anti-tumor agent is selected from the group consisting of anti-metabolites, anti-tumor antibiotics and alkylating agents.

12. In a method of treating one or more tumors in a tumor-bearing animal, the improvement which comprises administering to the tumor-bearing animal under an anti-tumor treatment an enhancer of anti-tumor effect which is an N^6-acyl-3'-deoxy-adenosine derivative represented by the formula:



wherein R^1 represents an acyl group and R^2 represents a hydroxyl group, a phosphoric acid residue or a phosphoric acid salt residue.

13. The method of treating one or more tumors as claimed in claim 12 in which the anti-tumor treatment comprises irradiation

of the tumor site of the animal, and the enhancer is administered to the animal before, simultaneously with, or after the irradiation.

14. The method of treating one or more tumors as claimed in claim 13 in which the enhancer is administered to the animal before the irradiation.

15. The method of treating one or more tumors as claimed in claim 13 in which the enhancer is administered after the irradiation.

16. The method of treating one or more tumors as claimed in claim 12 in which the anti-tumor treatment comprises administration to the animal of an anti-tumor agent, and the enhancer is administered before, simultaneously with, or after the administration of the anti-tumor agent.

17. The method of treating one or more tumors as claimed in claim 16 in which the anti-tumor agent is selected from the group consisting of anti-metabolites, anti-tumor antibiotics and alkylating agents.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

0068268

Application number

EP 82 10 5194

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
X	CHEMICAL ABSTRACTS, vol. 94, no. 21, 25th May 1981, page 767, no. 175450q, Columbus, Ohio, US & JP - A - 80 149 299 (YAMASA SHOYU CO, LTD)(20-11-1980) * Abstract *	1-5	A 61 K 31/70// C 07 H 19/16 C 07 H 19/20

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K 31/00
C 07 H 19/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-5

Claims searched incompletely:

Claims not searched: 6-17

Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (See article 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	20-09-1982	VERHULST

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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